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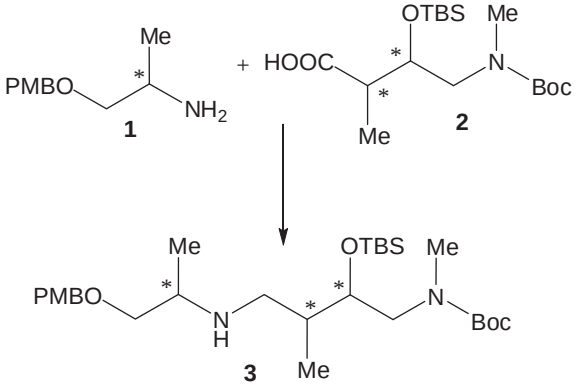
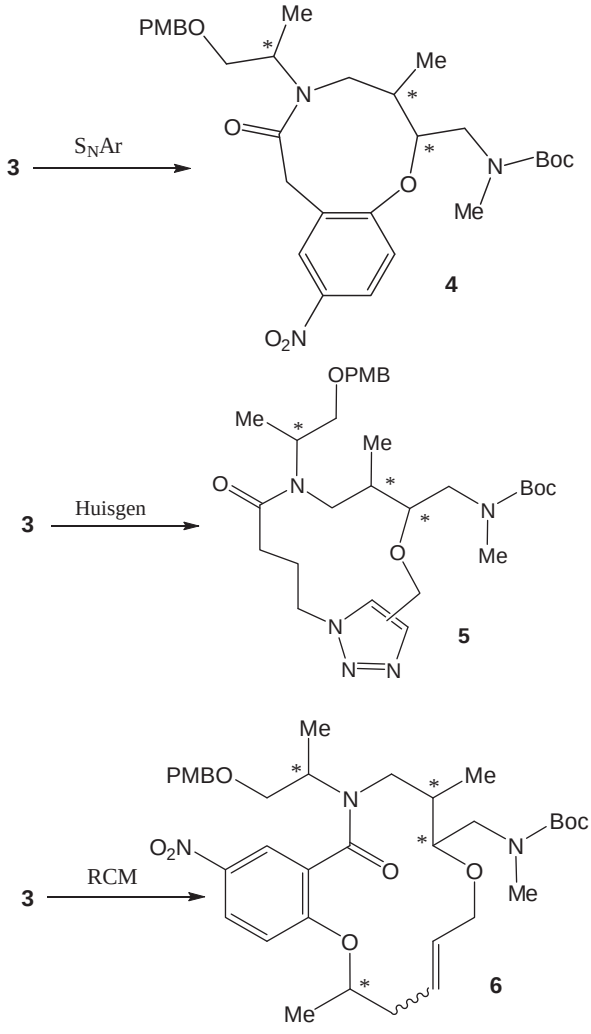
1. Current literature highlights

1.1. Aldol strategy for libraries of macrocyclic histone deacetylase inhibitors

It has been noted that compounds in libraries tend to be less complex than drug or natural product molecules as measured by sp^3 content. To address this deficit, an approach to a small molecule library has recently been described where there was an intention to increase structural and stereochemical complexity. In particular, the approach allowed access to a complete matrix of stereoisomers of macrocycles and medium-sized rings to allow investigation of stereo-structure activity relationships (SSAR).[1]



The diversity oriented synthetic approach employed a three-phase approach called build/couple/pair (B/C/P). The first step – the build phase – required the acquisition of stereochemically defined building blocks with suitable functionality for coupling. The building blocks were coupled to generate all possible stereoisomers, and in the final pair phase, the linear precursors were intramolecularly cyclised to give a diversity of ring systems. This approach gave access to both medium-sized (8–9 atom) ring systems and macrocycles with 12–14 atoms. As an illustration, all stereoisomers of the building blocks **1** and **2** were generated (the latter by stereocontrolled aldol condensations), and combined to give all 8 stereoisomers of the dimer **3**. Medium-sized rings (**4**) and macrocycles (**5** and **6**) were generated by nucleophilic aromatic substitution, Huisgen [3 + 2] cycloaddition and ring-closing metathesis (RCM) reactions.



Using SynPhase lantern solid supports, a library of >30,000 compounds were generated based on the 48 diverse scaffolds made using the B/C/P approach. For example, the 16 RCM scaffolds

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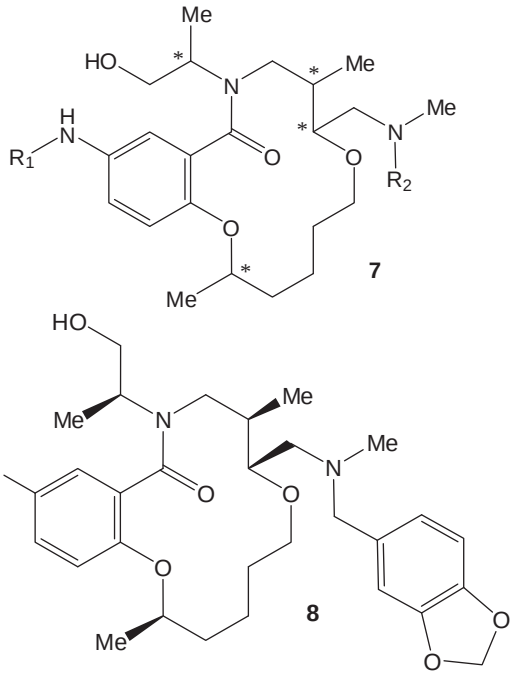
were the basis of a collection of 14,400 compounds. The library components were analysed by UPLC and purity assessed by UV detection at 210 nm, demonstrating an average purity of 81%. The compounds were screened in a variety of biochemical and cell-based assays, and several low micromolar inhibitors of histone deacetylase (HDAC) type 2 were identified.

In particular, the RCM macrolactams (**7**) generated the most interesting hits against HDAC 2. Thirty-two compounds exhibited inhibition >24% when tested at 17 μM, the most active of which were the result of reductive amination with piperonaldehyde at the R_2 position. In generating all stereoisomers of one preferred structure, it was found that the (2*S*,5*R*,6*R*,12*R*) isomer (**8**) had an IC_{50} value of 6.6 μM. This compound, designated BRD-4805, was resynthesized using solution phase methods and activity was confirmed against HDAC 2 although the compound was not selective over HDACs 1 and 3. BRD-4805 is distinguished from other reported HDAC inhibitors by its unique binding profile, showing mixed inhibition kinetics.



2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

No papers this month.

2.2. Solution-phase synthesis

Rapid access to the central tricyclic core of 4,5,6-trinems has been achieved by employing alkyne [2 + 2 + 2]-cyclotrimerisation as the key and final reaction in the synthesis. Introduction of different substituents to the structure was readily achieved and this approach was used to prepare a focussed library of trinem-like small molecules.[2]

The formation of a library of diverse macrocycles with different ring sizes from two easily accessible building blocks has been presented. Reacting diol precursors with electrophilic reagents led to 17-membered sulphites and 19-membered malonates in 34–79% yield. Double-reductive amination of dialdehyde analogues of the diol precursors gave 15-membered amines in yields ranging from 9% to 60%.[3]

The four component Ugi reaction of 2-furaldehyde, an alkenoic acid, an isonitrile and an amine affords rapid access to a family of acetylenic furan analogues, which on heating undergo an intramolecular Diels–Alder (IMDA) reaction yielding highly substituted tricyclic lactams in good to excellent yields (38–72% two-steps). This Ugi-IMDA reaction proved to be highly substituent tolerant across both the isonitriles and amines examined.[4]

2.3. Scaffolds and synthons for combinatorial libraries

A new phosphonotyrosine analogue, L-phosphonobromomethylphenylalanine (BrPmp), has been prepared as a new key component of inhibitors of protein tyrosine phosphatases. The BrPmp derivative was prepared as an Fmoc-protected amino acid which can be used in standard solid phase peptide synthesis.[5]

2.4. Solid-phase supported reagents

A new silica immobilised palladium–phosphine complex has been developed and found to be an efficient catalyst for Suzuki–Miyaura cross-coupling reaction under mild conditions. The supported catalyst could be reused at least 10 times without a significant loss of catalytic activity.[6]

2.5. Novel resins, linkers and techniques

A series of thieno[3,2-*b*]quinoline derivatives designed based on the A-278637 have been synthesised efficiently via one-pot three-component reaction under solvent-free and catalyst-free conditions. This approach provides a new compound library with potential biological activity for biomedical screening.[7]

A series of 4-aryl-cyclopenta[*b*]pyran derivatives, designed based on a natural product scaffold, were synthesised efficiently via a multi-component reaction under solvent-free and catalyst-free conditions. This chemistry has been used to generate a new compound library.[8]

2.6. Library applications

The electrochemical behaviour of an indole library of compounds, including several tryptophan and tryptamine derivatives previously demonstrated to be active against reactive oxygen species (ROS), has been investigated. A voltammetry study has been undertaken and the oxidation potential was correlated to the scavenging activity reported for these indoles.[9]

Tripeptides such as RGD and NGR are showing promising results for targeted drug delivery and in vivo imaging. An on resin Huisgen's 1,3-dipolar cycloaddition has been used to synthesise new cyclic RGD and NGR peptide analogues and preliminary binding assays of these new analogues by fluorescence polarisation indicated specific binding to purified CD13 (Aminopeptidase N) and cell lysates from MCF-7 and SKOV-3 cancer cell lines.[10]

A novel series of quinolinone-based adenosine A_{2B} receptor antagonists has been identified via high throughput screening of an encoded combinatorial compound collection. Synthesis and assay of a series of analogues highlighted essential structural features of the initial hit, and subsequent optimisation resulted in an A_{2B} antagonist which exhibited potent activity in cAMP accumulation and IL-8 release assays.[11]

Screening of a pteridine-based compound library led to the identification of compounds exhibiting immunosuppressive as well as anti-inflammatory activity. Optimisation afforded a series of 2-amino-4-*N*-piperazinyl-6-(3,4-dimethoxyphenyl)pteridine analogues, the most potent of which displayed low nM IC_{50} values in the Mixed Lymphocyte Reaction (MLR) assay.[12]

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Further reading

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